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Preparation and Evaluation of Intraoral Drug Delivery System for Rasagiline mesylate

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ABSTRACT
The aim of the present work was to prepare and evaluate a buccal film for intraoral delivery of Rasagiline. Formulations were prepared using 3^2 full factorial design to explore the effects of carbopol P 940 and sodium alginate (as independent variables) on mucoadhesive strength and drug release (as dependent variables). In addition to the above, the prepared films were also evaluated for surface pH, percentage moisture absorption (PMA), Percentage moisture loss (PML), folding endurance and content uniformity. The release profile data was subjected to curve fitting analysis to describe the release mechanism from the buccal films. The main effects and the interaction terms were quantitatively evaluated by quadratic model. The Rasagiline release was decreased with increase in both the polymers. Carbopol has more pronounced effect than sodium alginate on the mucoadhesive strength. The objective of the study is to optimize formulation with desirable mucoadhesive strength and drug release. The experimented values are in good agreement with expected values for the optimized formulation which demonstrate the feasibility of the model in the development of buccal film.

Keywords: Rasagiline, buccal film, Factorial design, intraoral drug delivery.

INTRODUCTION

The Intra oral route is one of the more preferred routes of the drug administration as it is convenient and, with certain drugs, may provide a more rapid onset of action. Intraoral dosage forms deliver the drug to the target sites for local or systemic drug delivery in the oral cavity include the following: buccal, sublingual, periodontal, periodontal pocket, peribuccal, perilingual, tongue (i.e., lingual), and gum (i.e., gingival). The various type of intraoral dosage forms include liquid (solution, sprays, syrups, injection, etc) semisolids (i.e. ointment pastes, etc.) and solid dosage forms (i.e. quick-dissolve and slow-dissolve tablets, sublingual tablet, lozenges, films, filament, gums, patches, microparticales, drug delivery devices, etc.). [1] Intraoral drug delivery overcomes hepatic first-pass metabolism and promotes rapid systemic delivery with improved bioavailability with selected drugs having the required physiochemical and biopharmaceutical characteristics.

Most of the research in this area has focused on targeting drug delivery to the highly absorptive nonkeratinized tissues of the buccal mucosa, as these regions are the primary absorptive tissues in the mouth. [1]

The oral mucosa provides accessibility to allow for the precise localization of the dosage form for targeted drug delivery. The noninvasive nature of administration, ease and convenience of dosing, precise localization and increased permeability of the buccal mucosa make this a promising route of delivery. Also, the rich supply of blood vessels and lymphatics in the buccal mucosa results in rapid onset of drug action. Drugs absorbed from the buccal mucosa may directly enter the systemic circulation by way of the jugular vein, minimizing the first-pass liver metabolism, and gastric acid- or enzyme-mediated degradation. The presence of food or variations in the gastric emptying rate has little or no influence on drug delivery by the buccal route. When compared to other mucosal delivery routes, buccal drug delivery offers a higher degree of control and reproducibility; it also allows the opportunity to remove the dosage form to terminate drug absorption, if necessary. [2] Literature reveals the use of sodium alginate in bioadhesive formulations [3] and carbopol as a mucoadhesive polymer in tablet [4], Patches and films. [5]

Rasagiline mesylate is an irreversible inhibitor of monoamine oxidase (MAO) used for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa. [6] It is selective for MAO type B over type A by a factor of fourteen. 1.561 mg Rasagiline mesylate is equivalent to 1 mg of Rasagiline. The absolute bioavailability of Rasagiline is about 36%. Steady-state half-life is 3 hours. [6] It undergoes extensive hepatic biotransformation. [7]

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MATERIALS AND METHODS

Rasagiline Mesylate is a gift sample from Apotex Research Pvt Ltd (Bangalore). Carbopol procured from Oxfored laboratory (Mumbai), Sodium alginate from S.D. fine chem. Ltd (Mumbai) and glycerin from Merck specialities private limited (Mumbai). Porcine buccal mucosa is obtained from local slaughter house.

Design of Experiments

Based on evaluation of prototype formulation, two polymers were found to be having predominant effect on bioadhesive strength and drug release. A 3^2 Full Factorial design was employed to study the effect of two independent variables (X1=% carbopol and X2=% sodium alginate) in three different concentrations on the dependent variables like bioadhesive strength and drug release. For carbopol 0.25, 0.5 and 0.75 % and for sodium alginate 2, 2.5 and 3% were decided as the levels to be studied for the factors based on the initial experimentation. Buccal films F1-F9 were prepared by varying the levels of the independent variables as required by the experimental design and factors levels were suitably coded [8] (Table 1). The amount of the remaining excipients was kept constant.

Table 1: Formulation variables and levels

Formulation No	Carbopol	Sodium alginate
F 1	-1	-1
F2	0	-1
F3	+1	-1
F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1
	-1= 0.25%	-1= 2.0%
	0=0.50%	0=2.5%
	+1=0.75%	+1=3.0%

Procedure for the preparation of blank buccal films

Solvent casting method is used for the preparation of buccal films. Carbopol 940, sodium alginate and glycerin required to prepare 40 ml of the polymeric solution are accurately weighed. Carbopol 940 was mixed with glycerin and then this mixture is dissolved in distilled water, heated to temp 60 ºC, after that Sodium alginate was added in this polymeric solution and volume make up to 40 ml with DW, then polymeric solution was poured in to a 90 mm diameter Petridis on level surface, surface was adjusted by spirit level. After poured in Petridish, polymeric solution was kept at room temperature for removal of air bubbles and drying was carried out at 55°C for 15 hours in hot air oven, solvent was allowed to evaporate at controlled rate by covering the petridish with inverted glass funnel, to avoid blistering effect on dried films. The films obtained were used as such or cut into a diameter of 1 cm for different evaluation studies.

Preparation of Drug loaded buccal films

Method of Preparation: Calculated amount of Rasagiline mesylate (1.98 mg/cm² of Rasagiline mesylate) was added in the polymeric solution; the drug is completely dissolved to form a clear solution and preceded as similar to that of blank film preparation. The composition of the polymeric films containing Rasagiline mesylate is given in the Table 2.

Preformulation Studies

***Ex-vivo* drug permeation study:**

Preparation of porcine buccal mucosa: This method was modified from Patel VM *et al.* [9] Buccal tissue of freshly slaughtered pigs was immediately placed in cold kerb's buffer and transferred to our laboratory.

The buccal mucosa were carefully separated from fat and muscles using micro dissecting forceps and scissors within 2 h and then were stored at refrigerator until it was used.

Drug permeation Studies: The drug permeation from the solution was studied using the Franz diffusion cell. The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell with internal diameter of 2.1 cm (3.46 cm^2 areas) with a receptor compartment volume of 30 ml. 30 ml of distilled water was placed in the receptor compartment. The donor compartment contained a solution of 5 ml of distilled water in which 5 mg of Rasagiline was dissolved.

The entire set up was placed over magnetic stirrer and temperature was maintained at 37°C by placing the diffusion cell in a water bath. 0.5 ml sample was collected at predetermined time intervals from receptor compartment and replaced with an equal volume of the distilled water. The samples were analyzed by High Performance Liquid Chromatography using C18 column. Mobile phase was 10% acetonitrile in triple distilled water, pH adjusted to 3.1 using orthoPhophoric acid, followed by detection at 265 nm. The Rasagiline mesylate concentration in the buccal mucosa permeates was corrected for sampling effects according to following equation [10]

$$C^1_n = C_n (V_T/V_T-V_S) (C^1_{n-1}/C_{n-1})$$

Where 'C^1_n' is the corrected concentration of the nth sample, 'C_n' is the measured concentration of Rasagiline mesylate in the nth sample, 'C^1_{n-1}' is the corrected concentration of Rasagiline mesylate in the (n-1) th sample, 'V_T' is the total volume of the sample drawn.

Table 2: Composition of Rasagiline mesylate Buccal Films

Ingredients	Formula No.								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rasagiline mesylate (mg)	127 mg	127 mg	127 mg	127 mg	127 mg	127 mg	127 mg	127 mg	127 mg
Sodium alginate	2%	2%	2%	2.5 %	2.5 %	2.5 %	3%	3%	3%
Carbopol 940	0.25%	0.5 0%	0.75%	0.25%	0.5 0%	0.75%	0.25%	0.5 0%	0.75%
Glycerine (% w/w of total polymer weight)	10 %	10 %	10 %	10 %	10 %	10 %	10 %	10 %	10 %
Distilled water (q. s.)	10 0%	100 %	10 0%	10 0%	10 0%	10 0%	10 0%	10 0%	10 0%

Drug-Excipient Interaction Studies

There is always possibility of Drug Excipient interaction in any formulation due to their intimate contact. IR spectroscopy is one of the most powerful analytical techniques, which offer possibility of chemical identification. The separate IR spectra of Rasagiline mesylate, sodium alginate, Carbopol 940 and physical mixture of Rasagiline mesylate, sodium alginate and Carbopol 94 of were obtained. Physical mixture prepared by ratio of Rasagiline mesylate: Polymers (10:90 %) mixed with spatula and in a polybag and samples are placed in vials then charged at 40°C and 75 % RH in stability chamber for 15 days. After 15 days the IR Spectra for initial sample and stability sample is done by using FTIR (Fourier transform infrared) spectroscopy.

Evaluation of Rasagiline Mesylate Buccal Films

Thickness, weight uniformity, folding endurance:

The thickness of the film was measured using Digital vernier calipers with a least count of 0.01 mm at different places of the films. The thickness was measured at ten different spots of the film and average was taken and SD was calculated.

For evaluation of film weight ten films of every formulation were taken and weighed individually on a digital balance. The average weights were calculated.

Folding endurance of the films was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. This test was done on five films. [11-12]

Drug content uniformity and surface pH

Three film units (1cm diameter) of each formulation were taken in separate 100 ml volumetric flasks, and 100 ml of distilled water was added, continuously stirred for 1h. The solutions were filtered and absorbance was measured in UV-spectrophotometer at 271.6 nm using blank film solutions prepare similarly as above and used as a reference sample.

The mucoadhesive films were allowed in contact with 1 ml of distilled water. The surface pH was noted by bringing a combined glass electrode near the surface of films and allowing equilibrating for 1 min. [13]

Percentage moisture absorption (PMA) and Percentage moisture loss (PML)

The percentage moisture absorption test was carried out to check the physical stability of the buccal films at high humid conditions. Three 1cm diameter films were cut out and weighed accurately, and then the films were placed in desiccator containing saturated solution of sodium chloride keeping the humidity inside the desiccator at 75 %. After 3 days the films were removed, weighed and percentage moisture absorption was calculated. Average percentage moisture absorption of three films was found. [14]

Percentage moisture absorption = (Final weight – Initial weight)/Initial weight × 100

Percentage moisture loss was also carried to check the integrity of films at dry condition. Three 1cm diameter films was cut out and weighed accurately and kept in desiccator containing fused anhydrous calcium chloride. After 72 hours the films were removed, weighed. Average percentage moisture loss of three films was found out. [14]

Percentage moisture loss = (Initial weight – Final weight)/Initial weight × 100

Bioadhesive strength

The strength required to detach the polymeric film from the mucosal surface was applied as measure of the bioadhesive performance. The apparatus was locally assembled and was a modification of the apparatus applied by Gupta *et al*. [15]

Each formulation, 3 films were tested for bioadhesive strength and average strength with standard deviation was calculated.

***In-vitro* Release Study**

For *in-vitro* release study modified diffusion cell was used. Receptor Compartment volume of the diffusion cell was 30 ml. A buccal strip of 1 cm diameter (containing 1 mg of Rasagiline equivalent to 1.561 mg Rasagiline mesylate) was fixed on the aluminium foil by using acrylate glue and it is placed between the donor and reservoir compartment such that the film faces Receptor compartment. Receptor compartment were filled with distilled water and small magnetic bead was placed. And this whole assembly kept on the water bath placed on the magnetic stirrer and in water bath temperature maintained at 37±0.5ºC. Periodically samples were withdrawn and same volume fresh medium was replaced. The aliquots were analysed spectrophotometrically at 271.6 nm. Each formulation, 3 films were tested for *in-vitro* release and average release was calculated.

Regression analysis

The effect of formulation variables on response variables were statistically evaluated by applying one way ANOVA using a commercially available software package "Design expert version 7.1.3" (Stat-Ease Inc).To describe the response curvature ,The design was evaluated by quadratic model, which bears the form of equation

$$Y = b1 + b2X1 + b3X2 + b4X1X2 + b5\ X1^2 + b6X2^2$$

Where, Y is the dependent variable, b1 is the arithmetic mean response of the 9 trials. Coefficient b2 is the estimated coefficient for the factor X1 and b3 is the estimated coefficient for the factor X2. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when 2 factors interact. The polynomial terms ($X1^2$ and $X2^2$) are included to investigate nonlinearity. The values of correlation coefficients were set to be statistically significant at 5% confidential interval.

RESULTS AND DISCUSSION

Preformulation Studies

***Ex-vivo* drug Permeation Studies**

Porcine buccal mucosa has been the most frequently chosen model for *in-vitro* permeation studies because of its similarity to human tissue and is available in large quantities from slaughterhouses. The *Ex-vivo* drug Penetration Studies carried out through the porcine buccal Membrane. Cumulative amount of Rasagiline permeated through the porcine buccal epithelium is shown in Fig. 1. The cumulative amount of Rasagiline mesylate permeated from the solution through the buccal epithelium was maximum of 72 % in 24 h.

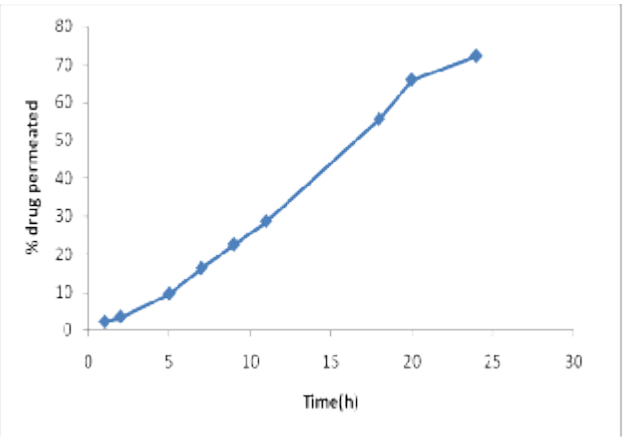

Fig. 1: Cumulative percentage permeation vs. Time in minute

Drug-Excipient Interaction Studies

The IR spectrum of pure drug, pure polymer and physical mixture of drug and polymers were studied. The characteristic absorption peaks of Rasagiline mesylate were

found at 3416.05 cm^{-1} for N-H stretching of secondary amines , at 1626.05, 1604.83, 1560.46 cm^{-1} because of N-H bending of secondary amines, at 2125.63 cm^{-1} for C ≡ C stretching , at 3279.1 cm^{-1} for C-H stretching , at 646.17 cm^{-1} for S- O bending and at 1479.45 cm^{-1} for CH_2- bending .The characteristic peak found in pure Rasagiline mesylate were also found in physical mixture of drug and polymer, so it indicates that there was no interaction between drug and excipients. The peaks obtained in the spectra's of each sample correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

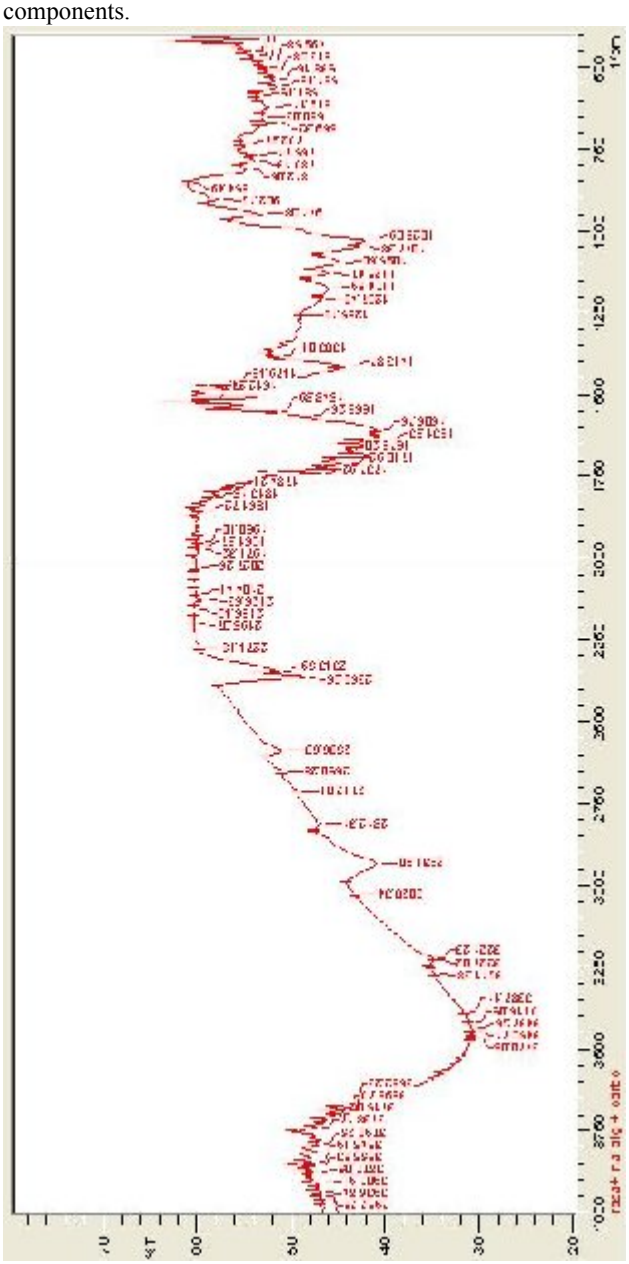

Fig. 2: IR Spectrum of Rasagiline mesylate + Carbopol 940 + sodium alginate

Evaluation of Rasagiline mesylate Buccal Films

Thickness, weight uniformity and folding endurance

The mean thickness of the buccal polymeric film prepared increases with increase in the amount of polymer percentage (Table 3). The order of film thickness was F9>F8>F6>F7>F5>F4>F3>F2>F1. The F9 had maximum thickness which had both Sodium alginate and Carbopol 940 at maximum concentrations.

Weight of the films was found to be in the range of 16.1 ±1.20 mg to 26.5 ± 1.58 mg (Table 3). As the proportions of the polymers are increasing, correspondingly the weight of film is increasing.

Films did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between plain films and drug loaded films. All films did not crack or broken after 300 times folding, so it reveals that the all films having satisfactory flexibility.

Surface pH and Content uniformity

The maximum surface pH from all the formulations was found to be 6.86 and the minimum was 6.71 (Table 3) which were near the salivary pH (5.5 to 7.0). The results reveal that all the formulations provide an acceptable pH in the range of 5.5 to 7.0 (salivary pH). Hence, they may not produce any local irritation to the oral mucosa.

The drug content uniformity values were between 109.8% and 96 % of the theoretical values (Table 3). The observed results of content uniformity indicated that the drug was uniformly distributed throughout the film.

PMA and PML

Checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for PMA and PML. The observed results of PMA and PML were shown in the Table 3. The observed PMA was in order of F9>F8>F6>F7>F5>F3>F4>F2>F1. This is observed that as the % of Carbopol 940 is increased PMA increased along with increase in Sodium alginate content. F9, F8 and F7 are films with 3% Sodium alginate with 0.75, 0.5and 0.25% Carbopol 940. Similarly set of F6, F4 and F3 are with 2.5% Sodium alginate with 0.75, 0.5 and 0.25% Carbopol 940. Set of F3, F2 and F1 are with 3% Sodium alginate with 0.75, 0.5 and 0.25% Carbopol 940. Amongst all the formulation the high value of PMA can be observed in and F9.The PMA of the mucoadhesive films were shown in Table 3 and it suggested that the films containing more amount of Carbopol 940 shows more PMA than the rest of the films, this would be due to more swelling of polymers and hold more amount of water in their network as carbomers are more hygroscopic in nature. [16]

The PML was found in the same order to that of PMA F9>F8>F6>F7>F5>F3>F4>F2>F1 due to the high degree of hygroscopicity of mucoadhesive polymer like Carbopol 940.

Bioadhesive strength

Bioadhesion, defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. [17]

The swelling state of the polymer has been reported to be crucial for its bioadhesive behavior. The Regression coefficient for Y1 is as follows

Muco adhesive strength (Y1) = 24.10209 + 1.78981 * Sod alginate + 2.42116 * Carbopol.

The Model F-value of 19.37 implies the model is significant. The sign and magnitude of main effcts signify the relative influence of each factor on the response. [18] The above equation reveals Bioadhesive strength increases with increase in the concentration of Carbopol as well as sodium alginate. Particularly, carbopol individually has more pronounced

Table 3: Mean thickness, weight, drug content, surface pH, PMA and PML of all films

S. No.	Formulation code	Thickness in mm ± SD (n=10)	Weight in mg ± SD (n=10)	Drug content (%) (n=3)	Surface pH (n=3)	PMA (n=3)	PML (n=3)
1	F1	0.151 ± 0.011	16.1 ± 1.20	106.2 ± 0.90	6.73 ±.014	1.893 ± 0.008	0.641 ± 0.006
2	F2	0.166 ± 0.015	17.2 ± 1.87	100.4 ± 1.06	6.72 ± .014	2.242 ± 0.045	1.127 ± 0.013
3	F3	0.180 ± 0.015	19.3 ± 1.25	102.8 ± 1.4	6.71 ± .014	3.101 ± 0.034	1.531 ± 0.011
4	F4	0.204 ± 0.016	21.5 ± 1.58	96.6 ± 0.53	6.81 ± .007	3.057 ± 0.019	1.332 ± 0.046
5	F5	0.221 ± 0.013	23.2 ± 1.32	99.1 ± 0.53	6.78 ± .014	3.266 ± 0.019	1.428 ± 0.028
6	F6	0.231 ± 0.014	23.9 ± 1.20	106.8 ± 0.53	6.77 ± .007	3.832 ± 0.042	1.942 ± 0.016
7	F7	0.222 ± 0.013	23.4 ± 1.35	096.0 ± 0.53	6.86 ± .007	3.450 ± 0.084	1.702 ± 0.010
8	F8	0.239 ± 0.010	24.9 ± 1.37	109.8 ± 0.91	6.83 ± .007	3.869 ± 0.011	2.688 ± 0.036
9	F9	0.256 ± 0.015	26.5 ± 1.58	108.0 ± 0.91	6.81 ± .007	4.512 ± 0.232	2.863 ± 0.022

Table 4: Bioadhesive Strength

S. No.	Formulation code	Bioadhesive strength (g)
1	F1	20.83
2	F2	21.67
3	F3	25.17
4	F4	21.17
5	F5	24.17
6	F6	25.50
7	F7	23.33
8	F8	26.83
9	F9	30.67

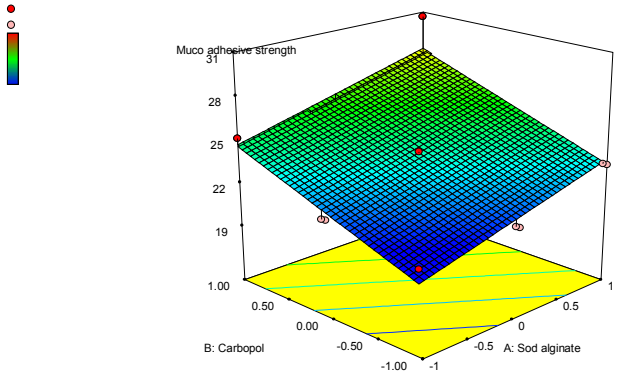

Fig. 3A: Response surface plot showing the effect of carbopol (X1) and Sodium alginate (X2) on mucoadhesive strength

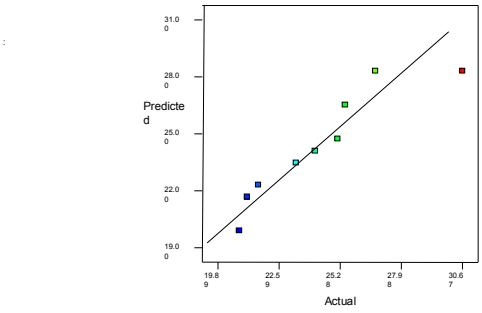

Fig. 3 B: Correlation between the actual and predicted values for Mucoadhesive strength

effect than sodium alginate on the mucoadhesive strength. This is in agreement with literature findings. [19-20]

The possible explanation for such a behavior is due to high concentration of carbopol upon exposure to moist surfaces, the pH of the microenvironment became acidic which caused an increase in mucoadhesion and carbopol forms secondary bioadhesion bonds with mucin and interpenetration of polymer chains in the interacial region , while other polymers only undergo superfacial bioadhesion [21] and the combined effect of factor X1 and X2 on mucoadhesive strength can further be elucidated by Fig. 3 A which represents the response surface plot and Fig. 3B which represents the observed values compared with that of the predicted values.

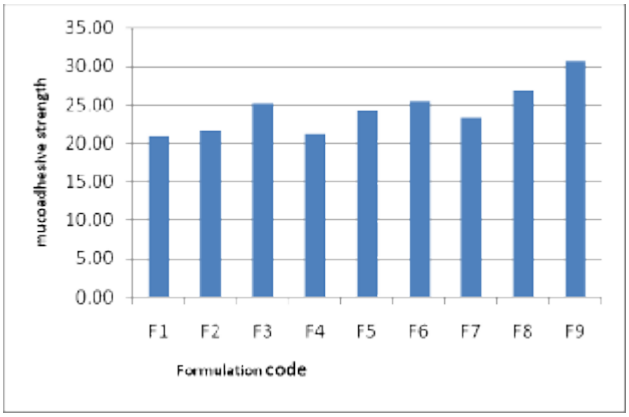

Fig. 3C: Barchart showing the mucoadhesive strength of all the formulations

The *Ex-vivo* mucoadhesive strength (bioadhesive strength) of polymeric buccal films was found to be in the following order F9>F8>F6>F7>F5>F3>F4>F2>F1. The *ex-vivo* mucoadhesive strength was increased linearly with increasing concentration of Carbopol 940 and not that much significant change with increase in the concentration of sodium alginate. The Carbopol 940 concentration (0.75%) and sodium alginate concentration (3%) polymeric buccal film showed highest adhesive strength. The increase in mucoadhesive strength may be due to the formation of a strong gel that penetrates deeply into the mucin molecules. Various mechanisms have been proposed to explain the in vitro bioadhesion or mucoadhesion phenomenon. These included electrical double layer, electrostatic attraction, hydrogen binding, Vander Waal's force, wetting, hydrophobic bonding, diffusion-interpenetration, physical entanglement and surface free energy. [17]

In-vitro Release Studies of Rasagiline mesylate from the buccal films

The model term Y2 (drug release at 3h) is found to be significant with an F value of 12.29 ($p<0.0081$) indicate the adequate fitting of quadratic model. In this case all the factors were found to be significant and the model describing the % drug release at 30 min can be written as

Drug release Y2 = 90.58 -7.33 * Sodium alginate -1.34 * carbopol

From the above equation we can conclude that the drug release decreases with increase in the polymer concentration and factor X1 (sodium alginate) has more significant effect than factor X2 (carbopol) on percentage drug release.

As the Proportion of polymer is increased from F1-F9, which causes the increase in viscosity of swollen polymer, which contributes more hindrance for drug diffusion and consequently decreases the release rate. As the carboxyl groups of carbopol dissociate highly at pH above their pKa, electrostatic repulsions between the negatively charged carboxyl groups cause uncoiling and expansion of the molecules, resulting in swelling and consequent gel formation. With further increase in polymer amount, thicker gel forms inhibiting water penetration, resulting in significant reduction in drug release. [19]

The combined effect of X1 and X2 can be further elucidated with the help of response surface plot. Fig. 4A and Fig. 4B represents the observed response values compared to that of predicted values. Highest value of Rasagiline release at 30 min was observed in formulation F 1 which has low value of both the polymers in the film.

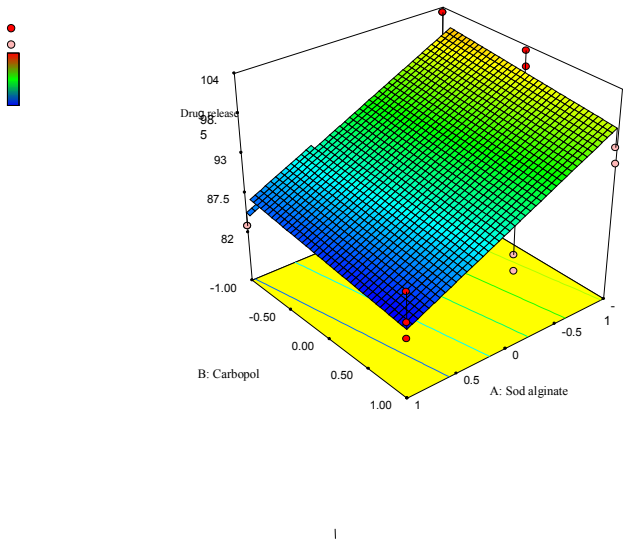

Fig. 4A: Response surface plot showing the effect of carbopol (X1)and Sodium alginate (X2) on drug release

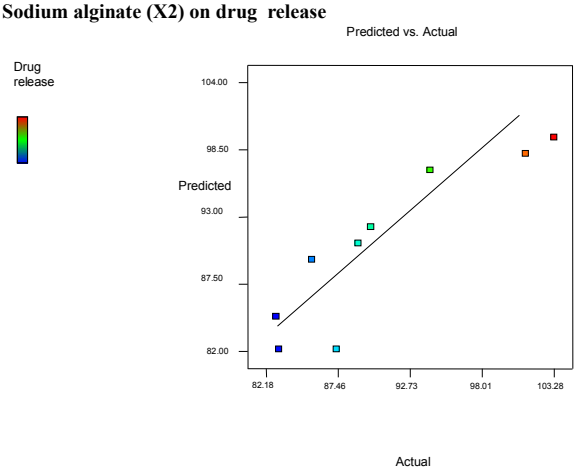

Fig. 4B: Correlation between the actual and predicted values for drug release

The release studies were performed up to 3 h. The results of *in-vitro* release studies are shown in the Table 5. Cumulative percentage release Vs. Time graphs were shown in the Figure (5, 6, and 7). The cumulative percentage drug release was compared in the formulations F1, F4 and F7 in which the percentage of Carbopol 940 is kept constant (0.25%), the percentage of Sodium alginate concentration was increased from F1, F4 and F7. The observed percent drug release was found to be 103.28 %, 89.85% and 82.91 which is in the order of F1>F4>F7 at all the time points correlating with the increase in the concentration of sodium alginate which controlled the release of Rasagiline mesylate from the films.

The cumulative percentage drug release was observed in the formulation F2, F5 and F8. The observed percent drug release was in the order of F2>F5>F8 at all the time points. After 3 h. the release was found to be 101.19 %, 88.93 % and 87.34 % for F2, F5 and F8 films respectively. In the above films Carbopol 940 concentration is kept constant (0.5%), the percentage of Sodium alginate was increased from F2, F5 to F8 which controlled the release of Rasagiline mesylate from the films.

The cumulative percentage drug release was observed in the formulation F3, F6 and F9. The observed percent drug release was in the order of F3>F6>F9 at all the time points. After 3 h. the release was found to be 94.20 %, 85.53 % and 83.11 % for F3, F6 and F9 films respectively. In the above films Carbopol 940 concentration is kept constant (0.75%), the percentage of Sodium alginate was increased from F3, F6 to F9 which controlled the release of Rasagiline mesylate from the films.

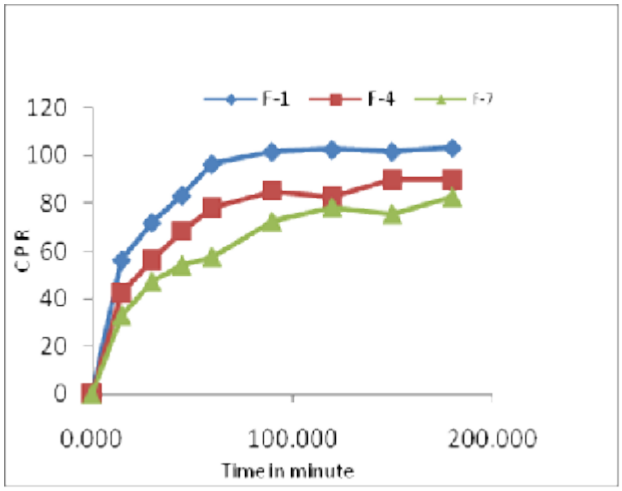

Fig. 5 : Cumulative Percentage Release of Rasagiline mesylate from F1, F4 and F7 buccal films

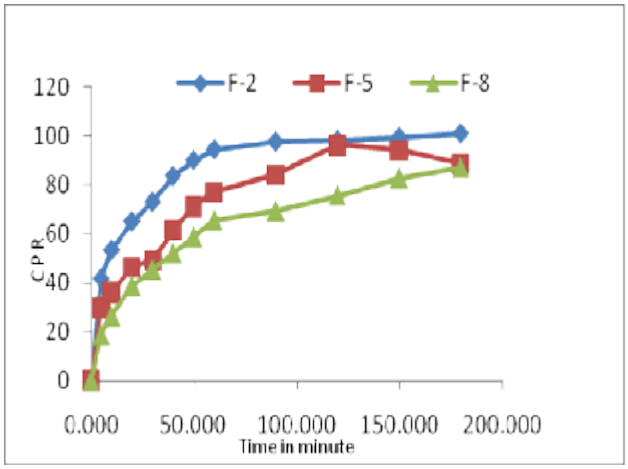

Fig. 6: Graph showing Cumulative percentage Release of Rasagiline Mesylate from Buccal films F2, F5 and F8

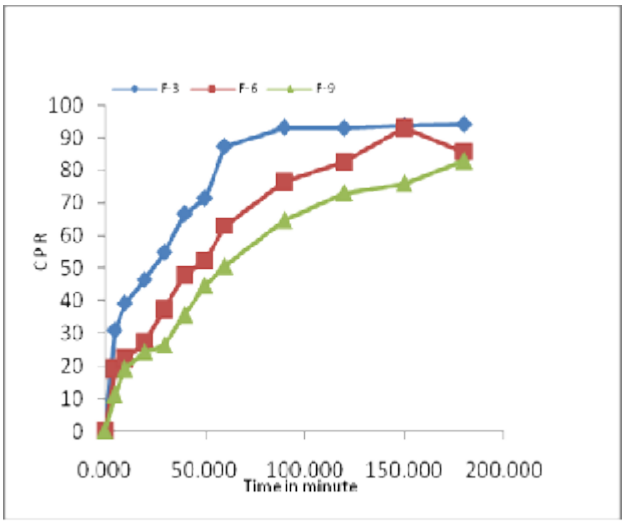

Fig. 7: Graph showing Cumulative percentage Release of Rasagiline Mesylate from Buccal films F3, F6 and F9

In vitro drug release mechanism

In vitro release characteristics of Rasagiline mesylate from buccal films showed decrease in percent released with an increase in the amount of polymer.

The release data of Rasagiline mesylate from various buccal films prepared was fitted to various mathematical models like

$Q_t = Q_0 + K_0 t$.....Zero order

$\ln Q_t = \ln Q_0 + K_1 t$.....First order

$Q_t = K_H t^{0.5}$.....Matrix (Higuchi)

$Q_t / Q_\infty = K_k t^n$ ……. Koresmeyer-Peppas

Where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$), Q_∞ is the amount of drug dissolved at $t = \infty$, K_0 is the zero order release constant, K_1 is the zero order release constant, K_H is the Higuchi dissolution constant, K_k is the Koresmeyer-Peppas drug diffusion coefficient. [19]

When the release data were fitted to Koresmeyer-Peppas release model and interpretation of release exponent values (n) enlightens in understanding the release mechanism from the dosage form.

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5< n <1.0	Non- Fickian diffusion
1	Case-II transport
1 >	Super Case-II transport

Table 5: *In Vitro* Release Kinetic Data of Rasagiline mesylate from Polymeric Buccal films

Formulation code	Zero order	First order	Higuchi	Koresmeyer-Peppas	
	r^2	r^2	r^2	r^2	Release exponent (n)
F1	0.9958	0.9798	0.9958	0.9951	0.3852
F2	0.9638	0.5838	0.9958	0.9969	0.33
F3	0.9872	0.9726	0.9608	0.9619	0.3933
F4	0.995	0.831	0.999	0.9491	0.3645
F5	0.9878	0.7125	0.9713	0.9651	0.3772
F6	0.9904	0.9808	0.954	0.9413	0.4865
F7	0.9135	0.8726	0.9608	0.9727	0.412
F8	0.9756	0.6282	0.9982	0.9986	0.4976
F9	0.9767	0.9213	0.9499	0.9636	0.5641

The results showed that all the films showed r^2 value range from 0.9135-0.9958 for zero order kinetics. All formulation F1 to F9 also yielded a quality adjustment with higuchi release model and when the release data were fitted to Koresmeyer-Peppas equation the release exponent values thus obtained was range from 0.33 to 0.5614. Formulation F1 to F8 exhibited fickian diffusion mechanism with an n value ranging between 0.33 to 0.4976 (Table 5) and formulation F9 exhibited non-fickian diffusion mechanism with an n value of 0.5641, these indicating the Rasagiline mesylate release from these buccal films were by both fickian and non fickian diffusion.

Optimization

The optimum formulation was selected based on the criteria of attaining 90% drug release in 3 hours with highest possible mucoadhesive strength.

Table 6: Comparison between the experimented (E) and predicted (P) values for the optimal formulation

Dependent variables	Experimented	Predicted
Bioadhesive Strength (g)	25.6	26.38
Drug release (%)	91.1	90.01

Upon comprehensive evaluation of feasibility search and, the formulation with polymer levels of Carbopol 0.75 % and sodium alginate 2.54% was suggested which fulfilled the required drug release and bioadhesive strength. To prove the reliability of the model, the new optimized formulation was prepared and evaluated for the responses .The results in Table 6 showed a good relationship between the experimented and predicted values, which confirms the practicability and validity of the model.

A 3^2 Factorial design was used to study the effect of carbopol and sodium alginate on mucoadhesive strength and the drug release from the prepared buccal films by applying optimization software. Both the polymer in higher concentration regulated the release of Rasagiline and carbopol has more significant effect than sodium alginate on Bioadhesive strength. The observed responses were in good agreement with the predicted values of the optimized formulation, there by demonstrating the feasibility of the optimization procedure in developing the buccal films of Rasagiline. Finally it can be concluded that with limited number of experiments an optimum formulation with required drug release and Bioadhesive strength can be designed with appropriate statistical experimental design and optimization technique.

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